The Preparation and Properties of Several Phenyl Alkyl Succinic Acids

THEOS JEFFERSON THOMPSON

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THE GRADUATE COLLEGE IN THE UNIVERSITY OF NEBRASKA
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

Lincoln, Nebraska,
1921

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The author desires to express his sincere gratitude to Doctor Fred. W. Upson, under whom this investigation was carried on, for his unfailing interest and valuable assistance.

THE PREPARATION AND PROPERTIES OF SEVERAL PHENYL ALKYL SUCCINIC ACIDS.

The original purpose of this investigation was the separation of the optical isomers of *iso*propyl-phenyl-succinic acid prepared by Avery and Upson.[1] To the present time this has not been accomplished although resolution was attempted with brucine, quinine, strychnine and cinchonine. During the course of the attempted resolutions, however, a number of incidental questions arose. Among these were the preparation of other substituted succinic acids, the difficulty of saponification of the nitrils of certain substituted succinic acids already referred to by Avery and Upson, and the structure of the sodium benzyl compound which results from the interaction of sodium amide and benzyl cyanide.

I. Preparation of Nitrils.

Preparation of alkyl phenyl-succino-nitril and of alkyl phenyl-succino-half-nitril half-ester was carried out by condensing alkyl cyanohydrines with benzyl cyanide by means of (1) sodium ethoxide, or methoxide and (2) esters of α-bromo fatty acids with benzyl cyanide by means of sodamide, respectively.

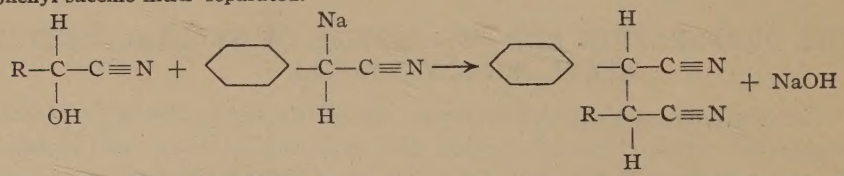
1. Alkyl Aldehyde Cyanohydrines with Benzyl Cyanide. Discussion.—When it was determined that *iso*propyl-phenyl-succinic acid could not be resolved, an attempt was made to prepare other substituted succinic acids, in the belief that optically active compounds might be resolved from them. The method of condensation employed was a modification of the one used by Avery and Upson[1] in the preparation of *iso*propyl-phenyl-succino-nitril. The condensations of the cyanohydrines of acetic aldehyde, *n*-propionic aldehyde, acetone, methylethyl-ketone and *iso*valeric aldehyde with benzyl cyanide were attempted in the order mentioned; but *iso*valeric-cyanohydrine was the only one that gave a condensation compound. The yield was very good in the case of the *iso*valeric -phenyl-succino-nitril; also in the case of *iso*propyl-phenyl-succino-nitril. As yet we

[1] Avery and Upson, *J. Am. Chem. Soc.*, **30**, 600 (1908).

have been unable to determine why we could not secure favorable results from the other cyanohydrines. It was first thought, as suggested by Higson and Thorpe,[2] that the proportional amount of sodium used was too large, but this was reduced far below the equimolecular proportion with the same results.

Experimental.—Since the operations in each case were in the main the same, only the condensation of *iso*valeric-cyanohydrine with benzyl cyanide will be described.

Eight g. of benzyl cyanide was added to 1.5 g. of sodium, which had been dissolved in an excess of methyl alcohol. To the sodium methoxide-benzyl cyanide solution, 8 g. of *iso*valeric-aldehyde-cyanohydrine was added. The mixture wa shaken several times and allowed to stand for several hours, whereupon large cyrstals of the *iso*valeric phenyl-succino-nitril separated.

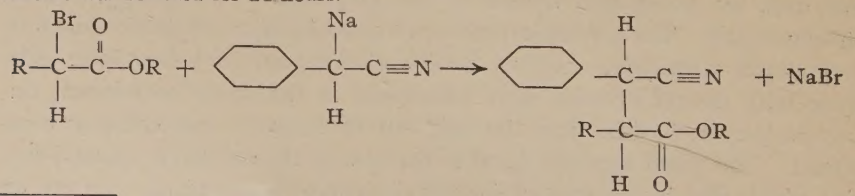


When it was believed that crystallization was complete, the crystals were collected, and dissolved in hot methyl alcohol. After this solution cooled, water was added until crystallization of the nitril occurred. The crystals were dried and weighed. Yield, 84%, much better than the yield obtained by Avery and Upson. Ethyl alcohol may be used in place of methanol, but is slower in reaction and the yield is slightly less.

2. Ethyl Esters of Alpha-bromo Fatty Acids with Benzyl Cyanide.

Discussion.—In 1910 Bodroux and Taboury[3] allowed sodamide to react with benzyl cyanide suspended in ether. By means of the reaction of alkyl halides on this sodium benzyl cyanide, they were able to prepare a number of derivatives. This method was adapted to the preparation of the substituted succinic acids, if α-bromo fatty acid esters were used in place of alkyl halides. In each reaction attempted, more or less satisfactory results were obtained. The yield was generally quite low.

Experimental.—Four g. of finely powdered sodamide was suspended in 40 cc. of absolute ether and to this 12 g. of benzyl cyanide was added in small amounts while the reaction mixture was cooled by running water. A moderate reaction occurred. Ammonia was evolved and the solution assumed a color varying from amber to red. After the reaction had subsided, the mixture was refluxed for 12 hours. To the sodium benzyl cyanide compound 21 g. of ethyl α-bromo-*iso*valerate was added in small amounts while the reaction flask was cooled in running water. After a vigorous reaction, the mixture set to a jelly-like mass. A large excess of absolute ether was added and the mixture was refluxed for 24 hours.



[2] Higson and Thorpe, *J. Chem. Soc.*, **89**, 1455 (1906).

[3] Bodroux and Taboury, *Compt. rend.*, **150**, 531–3 (1910).

When the reaction was complete, the ether solution was acidified with dil. hydrochloric acid. At this point, when an excess of sodamide was added, crystals of the half acid or dibasic acid separated. Whether they were the half-acid, or the dibasic acid, depended upon the character of the substituted groups. This will be discussed later. Usually an excess of sodamide was avoided and the acid solution was extracted several times with ether. Evaporation of the ether under diminished pressure on the boiling water-bath left an oily viscous residue in the flask. When conc. hydrochloric acid was added and the condensation product was refluxed for 8 hours, most of the oily residue disappeared; and, as the product cooled, small crystals separated. Since these crystals were insoluble in benzol, it was possible to extract the non-hydrolyzed residue, to evaporate the benzol under diminished pressure, and to continue the hydrolysis as before. Then the crystals were filtered from the diluted hydrochloric acid solution, dried, and dissolved in hot alcohol. The alcohol solut on was cooled and water added, whereupon crystals separated; m. p. (uncorr.) 172°. Titration of 0.0910 g. required 38.3 cc. of 0.01 *N* sodium hydroxide solution; the calculated amount for one hydrogen is 41.7 cc.

The crystals gave a positive test for nitrogen. The titration indicated that the compound had been hydrolyzed only partially. Since irregularity in saponification had already been observed,[2] the half-acid was placed in a bomb tube with conc. hydrochloric acid and heated at 135° for 24 hours. The crystalline substance obtained was washed into a beaker, and diluted with water to dissolve ammonium chloride. The crystals were then collected and dissolved in the smallest amount of hot alcohol. The addition of a large amount of cold water caused a copious crop of crystals to separate which melted sharply at 178°. Titration of 0.0722 g. required 59.0 cc. of 0.01 *N* sodium hydroxide solution; the calculated for two replaceable hydrogens is 61.2 cc. The yield was poor. A qualitative test for nitrogen was negative.

A mixed-melting-point determination was made with the acids obtained from ethyl α-bromo-*iso*valerate and *iso*butyl-aldehyde-cyanohydrine condensation compounds with benzyl cyanide. This mixture melted sharply at 178°, and therefore the compounds resulting from the two methods of preparation are identical.

When the hydrolysis was not attempted by means of refluxing but the oily residue was placed immediately in the bomb tubes, the crystals were found to be enveloped in an oily viscous mass which could be removed by shaking them with benzene.

This same method has been applied in the preparation of the following new substituted succinic acids, in addition to the one already discussed: (1) *n*-propyl-phenyl-succinic acid, prepared from ethyl α-bromo-*n*-valerate and benzyl cyanide; (2) ethyl-phenyl-succinic acid, prepared from ethyl α-bromo-*n*-butyrate and benzyl cyanide; (3) methyl-phenyl-succinic acid, prepared from ethyl α-bromo-propionate and benzyl cyanide.

II. Saponification.

Discussion.—It had been observed by Avery and Upson that the saponification of *iso*propyl-phenyl-succino-nitril was difficult. A similar difficulty of saponification of diphenyl-succino-nitril has been noted by a number of investigators.[4] So far as we have been able to determine,

[4] Reimer, (*Ber.*, **14,** 1802 (1881)) in speaking of saponifying dicyano-dibenzyl says: "Upon heating with alcoholic potassium hydroxide the substance yielded besides a resinous product only a very slight amount of acid..... A more sucessful saponification was accomplished by heating with concentrated hydrochloric acid at 200°."

Chalonay and Knoevenagel (*Ber.*, **25,** 289 (1892)) say: "By heating the substance

diphenyl-succino-nitril has never been hydrolyzed satisfactorily except under pressure at high temperatures. We believe this fact indicates a steric hindrance effect. This deduction is further borne out by the present investigation, because it has been impossible to saponify *iso*-propyl-phenyl-succino-nitril and *iso*butyl-phenyl-succino-nitril further than the half-acid by the usual methods; while *n*-propyl-, ethyl- and methyl-phenyl-succino-nitril are saponified with increasing ease by the usual methods. It should be noted that when the half-nitril half-ester of *iso*butyl or *iso*-propyl-phenyl-succinic acid was saponified, the nitril group remained intact, and from the method of condensation, this nitril group must be adjacent to the phenyl group. The preparation of a compound with an ester group adjacent to the phenyl was attempted by condensing ethyl ester of phenyl-bromo-acetic acid with aliphatic nitrils, but, as yet, positive results have not been obtained. It was hoped that this compound could be prepared so that we might determine, in a measure at least, whether the difficulty of saponification is entirely one of steric hindrance, or both steric hindrance and resistivity of the nitril group to saponification. In this connection Wren and Still[5] say: "The saponification of alpha (racemic) ethyl diphenyl-succinate with aqueous alcoholic potassium hydroxide proceeds normally....." This would indicate that the character of the nitril group as compared with the ester group entered into the question of saponification. Sulo Kilpi[6] after studying the rate of hydrolysis of aceto-, propiono-, *n*-butyro- and *n*-valero-nitrils with hydrochloric acid and alcohol and aqueous alkali states; "The velocity of hydrolysis increases in the same direction as does the negative character of the carbon atom of the carbonyl group determined according to the system of Michael." Although an accurate determination of the velocity of hydrolysis was not made, it has been definitely shown that the speed and ultimate complete saponification depends upon the character of the alkyl groups introduced. Whether the results are best explained by Michael's system, or on the basis of a steric hindrance effect, we cannot say at the present time. Either theory seems to offer a satisfactory explanation of the observed facts.

Experimental.

Hydrolysis of Iso-propyl-phenyl-succino-nitril by the Usual Methods.

(1) Five g. of *iso*propyl-phenyl-succino-nitril was refluxed with a 30% solution of sodium hydroxide for 8 hours. At this time, a portion of the solution was with-

(diphenyl-succinonitril) with concentrated hydrochloric acid at 150–160° diphenyl-succinic acid melting at 229–230° was obtained."

Wren and Still (*J. Chem. Soc.*, **107**, 445 (1915)) report: "It was further found that the hydrolysis of diphenyl-succinonitril at 200° by means of aqueous hydrochloric acid leads to the formation of meso-diphenyl-succinic acid."

[5] Ref. 5, p. 444.

[6] Kilpi, *Z. physik. Chem.*, **86**, 641–81 (1914).

drawn and acidified with hydrochloric acid, whereupon crystals separated. The crystals were dissolved in alcohol and when titrated indicated only a trace of acid. The refluxing was continued for 10 hours, when 0.0526 g. required 1.9 cc. of 0.1 *N* sodium hydroxide for neutralization; calc. for half-acid, 2.4 cc. The mixture was refluxed again for 8 hours, and upon titration indicated the presence of the half-acid. Further refluxing failed to hydrolyze the second nitril group.

(2) Five g. of the nitril was placed in a flask and 100 cc. of 95% alcohol added. Fifteen g. of solid sodium hydroxide was added to the alcohol solution and the whole refluxed for 12 hours. The alcohol was removed by vacuum distillation and the residue acidified with hydrochloric acid just dilute enough to dissolve the ammonium chloride. As in the first case, when the solution was acidified, a crystalline substance separated which, when titrated, showed the presence of one replaceable hydrogen. Further treatment with alcoholic sodium hydroxide gave the same result.

(3) Five g. of the nitril was dissolved in 25 cc. of methyl alcohol and an equal amount of water, to which was added 5 g. of sodium hydroxide. After this solution had been refluxed for 8 hours, 0.1143 g. required 3.2 cc. of 0.1 *N* sodium hydroxide solution for neutralization; calc. for one acid group, 5.13 cc. The refluxing was continued for 30 hours longer, but hydrolysis could not be carried beyond the half-acid stage.

(4) Five g. of the acid was placed in a flask with 100 cc. of conc. hydrochloric acid and the whole refluxed for 2 hours, when the water and acid were evaporated under diminished pressure. The residue was treated again with 100 cc. of conc. hydrochloric acid and refluxed for 8 hours. The crystals which separated from the cold dil. hydrochloric acid solution proved to be the half-acid.

Hydrolysis in every case was best brought about by the use of conc. hydrochloric acid. It was possible to hydrolyze completely the half-ester half-nitril of *n*-propyl-phenyl-, ethyl-phenyl- and methyl-phenyl-succinic acid in 16, 10 and 4 hours, respectively. The half-ester half-nitril of *iso*propyl-phenyl-succinic acid was hydrolyzed in much the same manner as the nitril and to the same degree. However, the ester group appeared to be more easily hydrolyzed than the corresponding nitril group.

III. Analysis and Properties of the Acids.

The acids are soluble in alcohol and ether and insoluble in cold water, benzol, petroleum ether, and chloroform. Their solubility in alcohol is a function of the number and relative positions of the carbons of the substituted alkyl groups. Methyl-phenyl-succinic acid is readily soluble in

TABLE I

ANALYSES, MELTING POINTS AND SOLUBILITIES OF THE ACIDS[7]

Acid	Hydrogen		Carbon		M. p.	Solubility in 100 g. water at 25° $\times 10^2$
	Calc. %	Found %	Calc. %	Found %	°C.	G.
*iso*Butyl-phenyl-succinic acid.....	7.02	7.11	67.02	66.84	183.4	13.3
*iso*Propyl-phenyl-succinic acid.....	6.77	7.05	66.1	66.16	178	20.6
n-Propyl-phenyl-succinic acid.....	6.77	6.87	66.1	66.00	213	2.11
Ethyl-phenyl-succinic acid.....	6.30	6.51	64.86	64.53	196	10.5
Methyl-phenyl-succinic acid.....	5.73	5.89	63.41	63.71	182	41.1

[7] Analyses by F. L. Herman and L. Porter.

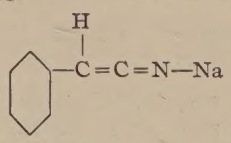
cold methyl or ethyl alcohol and cannot be precipitated from alcohol solutions by the addition of cold water as can the other acids of the series. It can be purified only by recrystallization from hot water. Microscopic examination of the crystals of the acids shows that each one possesses a characteristic crystalline form. The crystals of *iso*propyl-phenyl-succinic acid are especially beautiful.

Four determinations of the molecular weight of *iso*propyl-phenyl-succinic acid were made by the boiling-point method. The molecular weight determined from an average of the four is 241; that calculated, 236.

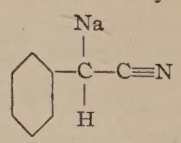
Structure of Sodium Benzyl-Cyanide Compound.

During the course of this investigation, a deposit of the sodium compound, formed by sodamide with benzyl cyanide in ether solution, was accidentally allowed to stand on a filter paper. When the ether evaporated auto-oxidation took place accompanied by considerable heat evolution. The heat of the reaction was sufficient to decompose the filter paper completely wherever the residue came in contact with it. It is thought the decomposition of a slight excess of sodamide liberated sufficient heat to start an auto-oxidation. Since such auto-oxidation reactions are in general characteristic of unsaturated compounds, we believe that the results observed indicate a state of unsaturation. The residue left after the reaction was complete was yellow in color with a cork-like texture.

A portion of the product was shaken with water in which it dissolved to give a clear solution. A small amount of the water solution gave a very positive reaction for sodium cyanide. Since the water solution showed no trace of immiscible liquids, such as benzyl cyanide, benzyl alcohol, or benzaldehyde, it was concluded that the remainder of the sodium benzyl-cyanide compound either must have volatilized during the auto-oxidation, or must be present in the residue in a soluble form. A small quantity of the cork-like residue was placed in a distilling flask and heated on an oil-bath. The temperature was raised gradually until as it approached 125° small crystals began to collect on the neck of the flask. The heating was continued until the temperature reached 180°. The crystals were recrystallized from hot water and proved to be benzoic acid. In view of these facts we suggest Formula I for the sodium benzyl cyanide compound,



(I).



(II).

and we believe the results observed can be explained better by this formula than by Formula II at present current in the literature.

In conclusion the facts seem to indicate that a state of unsaturation

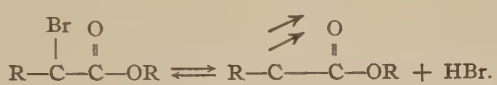
exists in the compound, and since the presence of sodium cyanide and benzoic acid has been shown, this unsaturation must exist between the carbon atoms.

The results and vigorousness of the reaction are probably best explained by (1) assuming that the unsaturation promotes the absorption of oxygen and the cleavage of the compound into benzaldehyde and sodium isocyanide, which always exist in equilibrium with sodium cyanide, cleavage at the ethenoid linkage being a common reaction especially in the presence of alkalies; (2) the fact that benzaldehyde in the presence of air, it is known, readily absorbs oxygen forming benzoyl hydrogen peroxide; and (3) the belief that the peroxide thus formed, being a very active oxidizing agent, interacts with benzaldehyde forming benzoic acid, thus accounting for the vigorousness of the reaction.

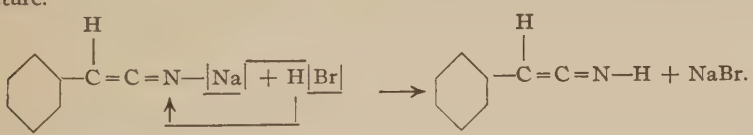
A simple explanation of the condensation reaction on the basis of the iso structure of the sodium benzyl cyanide compound is suggested by Nef's[8] ideas of the aceto-acetic ester and aldol condensations.

The condensation reactions are therefore outlined thus, using the suggested formula.

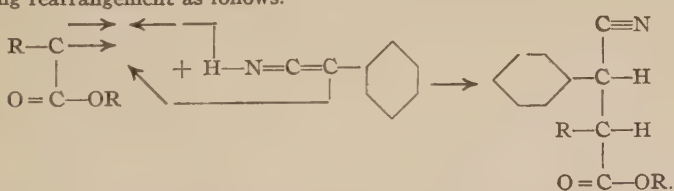
1. The bromo ester dissociates hydrogen bromide.



2. Hydrogen bromide reacts on the sodium benzyl-cyanide giving a ketene-imide structure.



3. The ketene-imide adds to the alkylidene derivative of the ester at the same time undergoing rearrangement as follows.



The work on the structure and properties of other metallic derivatives of benzyl cyanide is being continued.

Summary.

1. The following new substituted succinic acids were prepared: (1) methyl-phenyl-succinic acid, (2) ethyl-phenyl-succinic acid, (3) *n*-propyl-phenyl-succinic acid, (4) *iso*butyl-phenyl-succinic acid.

[8] Ref. *Ann.*, **298**, 218 (1897).

2. The preparation of the acid was brought about by two operations: (1) the condensation of molecules of proper constitution in the molecular proportions to synthesize the desired nitril or ester; (2) the hydrolysis of the nitril or ester.

3. Two methods were used to bring about the condensation: (1) aldehydes of the fatty acid series were converted to the cyanohydrines and condensed with benzyl cyanide by means of sodium ethoxide or sodium methoxide; (2) esters of α-bromo fatty acids were condensed with benzyl cyanide by means of sodamide.

4. The complete hydrolysis of the nitrils or esters of *iso*propyl- and *iso*-butyl-phenyl-succinic acid cannot be brought about by the usual acid or alkali methods, but these substances must be heated in a bomb tube at 130–140° for from 24 to 30 hours. This resistance to hydrolysis is probably due to a steric hindrance effect, to an electrochemical effect of the substituted alkyl group, or to a combination of the two effects

5. The general properties of each acid vary according to its constitution.

6. A new formula is suggested for the compound formed when sodamide reacts with benzyl cyanide in ether solution.